Maternal Cigarette Smoking and Invasive Meningococcal Disease: A Cohort Study Among Young Children in Metropolitan Atlanta, 1989–1996

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ABSTRACT

Objectives. This study assessed the association between maternal cigarette smoking during pregnancy and the risk of invasive meningococcal disease during early childhood.

Methods. Using a retrospective cohort study design, cases from an active surveillance project monitoring all invasive meningococcal disease in the metropolitan Atlanta area from 1989 to 1995 were merged with linked birth and death certificate data files. Children who had not died or acquired meningococcal disease were assumed to be alive and free of the illness. The Cox proportional hazards analysis was used to assess the independent association between maternal smoking and meningococcal disease.

Results. The crude rate of meningococcal disease was 5 times higher for children whose mothers smoked during pregnancy than for children whose mothers did not smoke (0.05% vs 0.01%). Multivariate analysis revealed that maternal smoking (risk ratio [RR] = 2.9; 95% confidence interval [CI] = 1.5, 5.7) and a mother's having fewer than 12 years of education (RR = 2.1; 95% CI = 1.0, 4.2) were independently associated with invasive meningococcal disease.

Conclusions. Maternal smoking, a likely surrogate for tobacco smoke exposure following delivery, appears to be a modifiable risk factor for sporadic meningococcal disease in young children. (*Am J Public Health*. 1999;89: 712–717)

Neisseria meningitidis is a major cause of bacterial meningitis and septicemia in the United States. Approximately 2600 cases of meningococcal disease occur annually in the United States, and attack rates are highest among young children.[1,2] The disease is often devastating; case-fatality rates range from 10% to 15%. Survivors may have long-term sequelae such as hydrocephalus and mental and physical handicaps.[1,2] In the United States, most meningococcal disease occurs sporadically and is caused by organisms of capsular serogroups B, C, Y, and W135.[1,3,4] The currently available polysaccharide meningococcal vaccines do not offer protection against serogroup B meningococci and are poorly immunogenic in children younger than 2 years.[5] Identification of groups at high risk for disease and identification of modifiable risk factors for invasive meningococcal disease are important for developing effective prevention strategies for this illness.

In recent years, at least 7 studies in Norway, England, and the United States have reported a link between exposure to tobacco smoke and meningococcal disease.[6–12] These studies have suggested that passive exposure of children to cigarette smoke increases their likelihood of acquiring invasive meningococcal disease severalfold. We report here the results of a cohort study to determine the association between cigarette smoking during pregnancy and other maternal and infant characteristics and the risk of developing sporadic invasive meningococcal disease during early childhood. In this study, we assumed that women who smoked during pregnancy continued to do so after giving birth, thereby exposing their children to cigarette smoke.

Methods

Data Sources and Subjects

We used a retrospective cohort design in which the past characteristics of the cohort were identified and their subsequent disease experience was reconstructed to the present. The occurrence of sporadic meningococcal disease in a cohort of children born in the metropolitan Atlanta, Ga, area (Clayton, Cobb, DeKalb, Douglas, Fulton, Gwinnett, Newton, and Rockdale counties) was reconstructed up to the completion of the child's third year of life or the end of the study period (September 31, 1996). We used Georgia's birth certificate database to identify all children born to mothers residing in the metropolitan Atlanta area between January 1, 1989, and December 31, 1995. The death certificates of all children 3 years and younger

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who died through September 31, 1996, were linked to the corresponding birth certificates. Initial linking was based on last names and birth dates of children, and further matching and validation were done by children's first names, mothers' maiden names, and fathers' last names. The birth and death certificates were matched for more than 90% of the eligible children. Data from prospective surveillance for invasive meningococcal disease[11] were used to identify cases of invasive meningococcal disease in these children. Cases of meningococcal disease were linked to the birth–death file by matching first and last names and date of birth. Children for whom information was missing were excluded from analysis.

The study cohort consisted of 283 291 children who were assumed to have resided in metropolitan Atlanta throughout the study period. The duration of follow-up was defined as the period between birth and diagnosis of meningococcal disease for children who developed the disease; the period between birth and death for children who died during follow-up without developing meningococcal disease; and the period between birth and September 31, 1996, or the third birthday, whichever came first, for the rest of the cohort. Children whose birth certificates were not matched to either death certificates or surveillance records for the meningococcal disease group were assumed to be alive and not to have developed meningococcal disease.

Identification of Cases

A case of invasive meningococcal disease was defined by the isolation of *N meningitidis* from either the blood or the cerebrospinal fluid of the patient. Isolates were serogrouped by standard laboratory techniques. Cases were identified as part of a laboratory-based surveillance project for meningococcal and other invasive bacterial infections in metropolitan Atlanta,[13–15] an area with 32 hospitals and a population of 2344 514 (1990 census). Initial case reports were obtained from hospital laboratories and infection-control practitioners. Laboratories were audited every 6 months to identify unreported cases and validate reported cases. Medical records of all audited patients were also reviewed.

Information Regarding Infant and Maternal Characteristics

Characteristics of infants and mothers were obtained from the birth certificate data file. Selected infant characteristics included sex, birthweight (<2500 g, ≥2500 g), and gestation at birth (<37 weeks, ≥37 weeks). Assessed maternal characteristics included age at delivery (<20 years, ≥20 years), race (White, Black, other), education (<12 years, ≥12 years), marital status (married, not married), and smoking of cigarettes during pregnancy (yes/no; if yes, the number of cigarettes smoked daily). The birth certificate and Georgia Medicaid claims databases were linked to determine the source of payment for prenatal care and delivery (Medicaid or other source). These variables were chosen because they may be confounders of an association between maternal smoking and sporadic meningococcal disease among children.

Analysis

Age-specific incidence was determined by the number of cases per total person-years of follow-up for each year of age. Univariate relationships between selected infant and maternal characteristics and invasive meningococcal disease were assessed by using the Fisher exact test. Variables found to be significantly associated with invasive meningococcal disease were entered in a multivariate model. To account for variable lengths of follow-up, Cox proportional hazards analysis was used to identify independent associations between selected risk factors and meningococcal disease. The proportional hazard assumption was assessed graphically by the SAS procedure LIFETEST[16] and by a test for the interaction between maternal smoking and time since the infant's birth.[17] Models were fitted by means of the SAS procedure PHREG.[16] Potential interactions between maternal race and maternal smoking during pregnancy and between maternal race and maternal education were also assessed. Because no cases occurred in children of mothers whose race was classified as "other," information from children of White women and Black women was used in hazards analysis.

Results

Fifty-five cases were identified. Two cases were in children born outside metropolitan Atlanta, and these cases were excluded. Four cases could not be linked to births in the study area or in Georgia, perhaps because of migration into the study area from another state. Information on maternal smoking during pregnancy was not available for these children. Information on maternal smoking during pregnancy or maternal education level was missing for 2 other cases. After we made these exclusions, we analyzed data from 47 cases.

Serogroup B *N meningitidis* accounted for 17 of the 47 cases (36%); 10 cases (21%) were serogroup C, 5 cases (11%) were serogroup Y, and 1 case (2%) was serogroup W135. Serogroup information was not available for 14 cases. Meningitis was diagnosed for 18 cases (38%). Four of the 47 cases (9%) died of meningococcal disease. No meningococcal disease outbreaks or secondary cases were noted in metropolitan Atlanta during the study period. The age-specific incidence was highest for children 1 year or younger (Table 1).

The proportion of children who acquired invasive meningococcal disease did not differ significantly by sex, gestation at birth, abnormal conditions, or mother's race, but several variables were significant in univariate analyses (Table 2). The proportion of children acquiring meningococcal disease was greater for teenaged mothers than older mothers (0.04% vs 0.01%, $P = .003$); unmarried mothers than married mothers (0.03% vs 0.01%, $P = .008$); mothers whose prenatal care and/or delivery was paid for by Medicaid than mothers whose prenatal care and/or delivery was paid for by another insurer (0.03% vs 0.01%, $P = .002$); mothers with fewer than 12 years of education than mothers with more than 12 years of education (0.04% vs <0.01%, $P = .00001$); and mothers who reported smoking during pregnancy than mothers who reported not smoking during pregnancy (0.05% vs 0.01%, $P = .00001$).

Among children of White mothers, the proportion acquiring meningococcal disease was significantly higher for those whose mothers were young, not married,

TABLE 1—Incidence of Invasive Meningococcal Disease by Age of Infant: Metropolitan Atlanta, Ga, 1989–1996

Age Interval of Children, y	No. of Children	Person-Years of Follow-Up	No. of Cases	Incidence Rate[a] (95% Confidence Interval)
0–1	283 291	279 761	36	12.8 (9.3, 17.8)
1–2	270 191	248 985	5	2.0 (0.8, 4.8)
2–3	228 534	207 692	6	2.9 (1.3, 6.4)

[a]Incidence of invasive meningococcal disease per 100 000 person-years.

TABLE 2—Univariate Relation Between Selected Infant and Maternal Characteristics and Invasive Meningococcal Disease: Metropolitan Atlanta, Ga, 1989–1996

Characteristic	All Children (n = 283 291)		White Children (n = 163 501)		Black Children (n = 110 770)	
	No. of Children	No. With Meningococcal Disease (%)	No. of Children	No. With Meningococcal Disease (%)	No. of Children	No. With Meningococcal Disease (%)
Sex of child						
Female	138 367	19 (0.01)	79 506	13 (0.02)	54 480	6 (0.01)
Male	144 924	28 (0.02)	83 995	18 (0.02)	56 290	10 (0.02)
Birthweight, g						
<2500	23 397	6 (0.03)	9137	4 (0.04)	13 664	2 (0.01)
≥2500	259 894	41 (0.02)	154 364	27 (0.02)	97 106	14 (0.01)
Gestation at birth, wk						
<37	29 517	7 (0.02)	12 893	4 (0.03)	15 962	3 (0.02)
≥37	253 774	40 (0.02)	150 608	27 (0.02)	94 808	13 (0.01)
Abnormal conditions in newborn[b]						
Yes	10 460	3 (0.03)	5196	2 (0.04)	5024	1 (0.02)
No	272 831	44 (0.02)	158 305	29 (0.02)	105 746	15 (0.01)
Mother's race						
White	163 501	31 (0.02)	...	...	...	...
Black	110 770	16 (0.01)	...	...	...	...
Other/unknown	9020	0 (0.00)	...	...	...	...
Mother's age at delivery, y						
<20	34 398	13 (0.04)[a]	12 550	10 (0.08)[a]	21 367	3 (0.01)
≥20	248 893	34 (0.01)	150 951	21 (0.01)	89 403	13 (0.01)
Mother's marital status						
Married	191 614	23 (0.01)[a]	140 918	18 (0.01)[a]	42 708	5 (0.01)
Not married	91 677	24 (0.03)	22 583	13 (0.06)	68 062	11 (0.02)
Mother received Medicaid						
Yes	76 712	23 (0.03)[a]	25 834	17 (0.07)[a]	49 059	6 (0.01)
No	206 579	24 (0.01)	137 667	14 (0.01)	61 711	10 (0.02)
Mother's education, y						
<12	48 668	21 (0.04)[a]	23 766	16 (0.07)[a]	23 280	5 (0.02)
≥12	234 623	26 (0.01)	139 735	15 (0.01)	87 490	11 (0.01)
Mother smoked during pregnancy						
Yes	29 267	16 (0.05)[a]	19 883	11 (0.06)[a]	9234	5 (0.05)[a]
No	254 024	31 (0.01)	143 618	20 (0.01)	101 536	11 (0.01)

[a]Proportions of children acquiring meningococcal infection are significantly different between at least 2 levels of the characteristic (Fisher exact test, $P < .05$).
[b]Abnormal conditions diagnosed in the newborn included anemia, injury during birth, fetal alcohol syndrome, respiratory distress syndrome, meconium aspiration syndrome, seizures, and other or unclassified conditions.

received Medicaid, or had fewer than 12 years of education (Table 2). For children of White mothers and African American mothers, the proportion acquiring meningococcal disease was significantly increased by maternal cigarette smoking during pregnancy.

Cox proportional hazards analysis indicated that children of mothers who smoked during pregnancy were 2.9 times more likely to acquire meningococcal disease than were children of mothers who did not smoke during pregnancy (Table 3). No significant interaction between race and maternal smoking status was found in determining risk for meningococcal disease (data not shown). In addition, examination of maternal smoking as a time-varying covariate (data not shown) indicated that the association between maternal cigarette smoking and risk for meningococcal disease did not significantly differ ($P = .552$) between a child's first year of life and the second and third years of life. After the effect of smoking during pregnancy was accounted for, no significant dose–response relation between the number of cigarettes smoked and risk for meningococcal disease was found (data not shown). Compared with children of mothers with 12 or more years of education, children of mothers with fewer than 12 years of education were 2.1 times more likely to acquire meningococcal disease. Although interaction between race and maternal education level was significant in determining the risk for meningococcal disease (data not shown), the number of cases was too small to allow reliable determination of risk by race.

The fraction of meningococcal disease attributable to exposure to cigarette smoke (for which maternal smoking during pregnancy was a proxy) was similar for all children, of both White mothers and African American mothers (Table 4).

Discussion

Our findings are consistent with the results of previous studies[6–12] and indicate that exposure to maternal cigarette smoking is a risk factor for sporadic meningococcal disease in young children. The rate of invasive meningococcal disease was 5 times higher for children of mothers who reported smoking during pregnancy than for children of mothers who did not smoke during pregnancy. This relation persisted when children of White mothers and children of African American mothers were examined separately. Maternal cigarette smoking during pregnancy was also independently associated with invasive meningococcal disease in multivariate analysis. After factors reflecting social and economic status were adjusted for, children of mothers who smoked during pregnancy were 2.9 times more likely to acquire invasive meningococcal disease than were children of mothers who did not smoke

TABLE 3—Associations of Selected Infant and Maternal Characteristics to Invasive Meningococcal Disease in Early Childhood: Metropolitan Atlanta, Ga, 1989–1996

Characteristic	Risk Ratio[a]	95% Confidence Interval
Mother's age, y: <20 vs ≥20 (reference)	1.52	0.71, 3.25
Mother's race: White vs Black (reference)	1.8	0.87, 3.58
Mother received Medicaid	1.54	0.80, 2.99
Mother married	0.70	0.33, 1.45
Mother smoked during pregnancy	2.93[b]	1.52, 5.66
Mother's education, y: <12 vs ≥12 (reference)	2.07[b]	1.02, 4.20

[a]Risk Ratio estimated by Cox proportional hazards model. All characteristics are adjusted for other characteristics in the table.

TABLE 4—Attributable Fraction of Invasive Meningococcal Disease Among Children Due to Maternal Cigarette Smoking During Pregnancy: Metropolitan Atlanta, Ga, 1989–1996

	Fraction Attributable to Maternal Smoking[a]
All children	0.26
Children of White mothers	0.26
Children of African American mothers	0.25

[a]Attributable fraction was calculated with the following formula: attributable fraction = [(incidence among all children in the cohort) – (incidence among children of mothers who did not smoke)] / [incidence among all children in the cohort]. Incidence = number of cases per 100 000 person-years.

during pregnancy. Approximately one quarter of invasive meningococcal disease among children could be attributed to passive exposure to cigarette smoke.

Several case–control studies[6–12] have linked exposure to cigarette smoke with invasive meningococcal disease. In one study in the United Kingdom, children younger than 5 years who were exposed to cigarette smoke at home were 4.5 times more likely to acquire meningococcal disease than were controls.[9] These differences remained statistically significant even after control for social class. A dose–response relation was found between the number of cigarettes smoked at home and the likelihood of invasive meningococcal disease. Fischer et al. have reported that during an outbreak of serogroup B disease in the Pacific Northwest among children younger than 18 years, cigarette smoking by the mother was the strongest independent risk factor (odds ratio = 3.8) for invasive meningococcal disease.[8]

Mechanisms that may determine the increased risk of meningococcal disease as a result of cigarette smoke exposure include the deleterious effects of cigarette smoke on mucosal integrity and the immune system.[8] Cigarette smoke depresses respiratory mucus secretion and bronchial ciliary activity and may reduce the effectiveness of the respiratory mucosa to act as a protective barrier against bacterial pathogens.[6,18–20] Exposure to cigarette smoke adversely affects macrophage activity and neutrophil function[21–23] and may indirectly increase the risk for meningococcal infection by predisposing children to viral respiratory infections.[24] Concurrent viral upper respiratory tract infections have been linked to meningococcal disease.[25–27] Several studies have implicated cigarette smoking as a risk factor for increased nasopharyngeal carriage of *N meningitidis*.[14,29–36] Therefore, children exposed to smokers may have a high likelihood of exposure to the pathogen, a high rate of carriage acquisition, or prolonged carriage of *N meningitidis*.

The age-specific incidence we found (highest for infants 1 year and younger) was consistent with previous reports that meningococcal attack rates are highest during the first year of life.[1,2] The incidence among 1- to 2-year-old and 2- to 3-year-old children (2.0 and 2.9 per 100 000 person-years, respectively) were also consistent with previous estimates.[1,2] National estimates for annual incidence of meningococcal disease for people of all ages is about 1 in 100 000 persons.[1,35] Our finding that serogroups B and C accounted for most cases was also consistent with national estimates reported close to or during the time of our surveillance.[1,35]

Although meningococcal disease has been reported to have a higher incidence among males than females and among Blacks than Whites,[1,35] we found no significant association by sex or race. Previous studies have reported an association between low socioeconomic status and meningococcal disease[6,9,36,37] because of an increased likelihood of acquiring meningococcal infection through factors such as increased household crowding and poor nutrition.[6,9,38–40] The level of educational attainment is commonly used as a proxy for socioeconomic status.[41] In our cohort, low maternal education level was independently associated with increased risk for invasive meningococcal disease for young children. Young maternal age at delivery, being an unmarried mother, and receiving Medicaid are also associated with low socioeconomic status, and in our cohort these factors were univariately associated with meningococcal disease in all children and in children of White mothers.

One limitation of this study is that the number of cases of invasive meningococcal disease was small, considering the breadth of the study population. We did not account for out-migration from the study area and may have missed counting some meningococcal cases. However, because the incidence of the disease was very low and the median follow-up duration for most children was 3 years (most cases occurred within the first year of life), movement of participants out of the study area is unlikely to have strongly influenced our findings. Another limitation is that cigarette smoking by the mother during pregnancy was identified through self-reported information acquired from birth certificates. A total of 10.3% of all mothers were reported to have smoked during pregnancy, and the rate was higher among White mothers than Black mothers (12.2% vs 8.3%). Using data from a postdelivery mail survey of a sample of women who gave birth in Georgia, epidemiologists recently estimated that about 34% of women who smoke during pregnancy do not have this fact documented on the child's birth certificate.[42] In addition, underreporting of smoking may be greater among Black women and women with higher education levels.[42] However, underreporting of maternal smoking would bias the potential association between smoking and meningococcal disease toward the null.

Because we could not directly measure the passive exposure of children to cigarette smoke, we assumed that mothers who reported smoking during pregnancy continued to smoke after giving birth. Studies have shown that most women who smoke at any time during pregnancy do so throughout pregnancy, and among those who quit smoking during pregnancy, most relapse shortly after giving birth.[42–45] Relapsers who report they

did not smoke during pregnancy would decrease the apparent magnitude of the identified risk between passive tobacco smoke exposure and meningococcal disease. Thus, a concerned mother may stop smoking during pregnancy and be reported as a nonsmoker, but she may resume smoking after delivery and unknowingly place her infant at increased risk for invasive meningococcal disease. These findings, in addition to the fact that adverse health effects during infancy can result from exposure to cigarette smoke in utero,[46] suggest that our findings are valid. Further, this study did not account for the exposure of children to cigarette smoke from persons in the household other than the mother.

One strength of our study is that all resident cases of invasive meningococcal disease were identified through a laboratory-based active surveillance system, and periodic audits were used to optimize the accuracy of detection. Studies have shown that, compared with passive surveillance systems, laboratory-based active surveillance for meningococcal disease is more accurate and able to identify twice as many cases.[47,48] The use of birth certificate data allowed the examination of several infant and maternal characteristics; the reporting accuracy of a number of these has already been evaluated. Our study illustrates how the linking of information from birth and death certificate databases to data from a population-based surveillance system for disease can be used to follow a birth cohort. For low-incidence diseases, this methodology may provide a simple, low-cost, yet powerful approach for assessing population-based rates by selected characteristics, computing relative risks, and examining trends. Moreover, this methodology permits an efficient approach to evaluating the effect of strategies to reduce risk factors such as maternal smoking and any changes in their association with meningococcal or other disease.

Maternal smoking during pregnancy has been associated with several adverse health effects on the fetus and infant, including prematurity, low birthweight, and sudden infant death syndrome.[46] Studies have shown that passive exposure to cigarette smoke increases a child's susceptibility to various infections.[49–51] Our findings support recent reports linking exposure to cigarette smoke with increased risk for invasive meningococcal disease in young children, and they add to the impetus for promoting smoking cessation among pregnant women and mothers. Health care providers and the general public need to be informed that cigarette smoking may be a strong risk factor for meningococcal disease. Smoking prevention can form an integral part of efforts to prevent meningococcal disease. At least 2 Web sites (University of Illinois at Urbana and National Meningitis Trust Fund) provide information on meningitis prevention and indicate that avoidance of exposure to cigarette smoke may reduce the risk for acquiring the disease. Because the association between exposure to cigarette smoke and invasive meningococcal disease has implications for public health, this research should be replicated in other geographic areas where meningococcal disease surveillance is occurring. □

Contributors

H. R. Yusuf planned the study, analyzed the data, and wrote the paper. R. W. Rochat and D. S. Stephens co-supervised study planning and implementation. W. S. Baughman developed the meningococcal disease active surveillance database and assisted with study design. P. M. Gargiullo assisted with statistical analysis and study design. B. A. Perkins assisted with planning of study and interpretation of results. M. D. Brantley assisted with matching birth and death record databases to develop a follow-up cohort, matching meningococcal cases to the cohort, and designing the study. R. W. Rochat, D. S. Stephens, W. S. Baughman, P. M. Gargiullo, B. A. Perkins, and M. D. Brantley contributed to writing the paper. All 7 authors are guarantors for the integrity of the research.

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